

REMARKS

The Applicants will now address the Examiners' rejections in the order presented in the office action.

Claim Rejections-35 USC 112, 2nd paragraph

Claim 7 is rejected under 35 USC §112, second paragraph, as being definite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4, the base claim, has been amended to reflect the Examiner's suggestion, and now recites "...wherein said adenoviral vector..." Applicants believe that the rejection is now obviated.

35 USC 103(a) Rejection

Claims 1, 4, 5, 7, 8, 11, 12, 14, are rejected under 35 USC § 103(a) as being unpatentable over McCormick I (US Patent NO. 5,666,178) or McCormick II (US Patent No. 5,801,029) taken with Yu or Fines.

As the Examiner has stated, both McCormick references teach an adenovirus having a mutation in the E1a region, which mutation causes a loss of RB binding to the protein encoded by the E1a region. Thus, such viruses preferentially target neoplastic cells lacking RB function. Importantly, the Examiner has further noted that neither McCormick I nor II, show the use of an E2F responsive promoter which controls the expression of an early adenoviral gene.

The Examiner, referring to McCormick I and II, has stated that Yu teaches the same.

Finally, the Examiner has cited Fine and stated that he teaches an adenoviral vector that can be used to carry an E2F responsive promoter operably linked to a heterologous gene to select against malignant cells *in vivo*.

Applicants respectfully submit that the Examiner is using hindsight to reject Applicants' claims, which, of course, is not permissible. It is worth recalling that an obviousness determination must be made at the time Applicants make their invention. For example, In *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983), it is stated:

"To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."

That is, obviousness cannot be established by a hindsight combination of references to produce Applicants' claimed invention. See also, In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed.Cir.1991), which stands for the proposition that it is the prior art itself, and not Applicants' achievement, that must establish the obviousness of the combination.

Clearly, Applicants' view is that the Examiner has combined *three* references, and is applying them in hindsight to reject their claims. Nowhere do any of the references show or suggest what Applicants are claiming. Particularly, none of the references claim "an adenoviral vector comprising an E2F responsive transcriptional nucleotide regulatory site that controls the expression of an early adenoviral gene, and a mutation in the E1a region of said adenoviral vector, which mutation causes a loss of RB binding to the protein encoded by the E1a region."

To support the Applicants' position, the Examiner is referred to a paper (Johnson, et al., Cancer Cell, Vol1, 325-337, May 2002) by the inventors and their co-workers where they study the invention viruses and state:

"These results demonstrated that: (1) the E2F1 promoter was active in the context of the left end of the adenoviral genome, and (2) its activity was responsive to pRB-pathway status ONLY in combination with delta CR2 mutant alleles and NOT wild-type E1A (emphasis added).

Furthermore, this statement needs to be considered alongside a statement made by Paul Hallenbeck and his co-workers, last two paragraphs of an article in Cancer Research (See: Jabubczak, et al Cancer Research vol. 63, 1490-1499, April 1, 2003). There they discuss the work of Johnson et al, mentioned above and published in Cancer Cell, and compare it to their own work, stating that there are differences:

“One is that the CR2 mutation may not be critical for oncolytic adenoviral vectors targeting RB pathway defects because we and Tsukudaa et al,(26) demonstrate selectivity with vectors containing a wtE1A coding region.”

This is exactly the opposite of what the Applicants have discovered and now claim. Clearly, the statement by Hallenbeck is a strong indication of the unobvious nature of Applicants' invention.

Furthermore, additional support for this position is the reference that Hallenbeck makes to Tsukudaa et al ., (Cancer Res., 62: 3438-2447, 2002). Tsukudaa's scientific findings were similar to Hallenbeck's. Thus, Hallenbeck's and Tsukudaa's papers both stand for, and support the unobviousness of Applicants' invention. Indeed, both of these references teach away from Applicants' claims.

Based on the above, Applicants respectfully submit that none of the cited references, McCormick I or II, Yu, or Fine render Applicants invention obvious, and request that the rejection be withdrawn

Claims 1, 4, 5, 7, 8, 11, 12, 14, are rejected under 35 USC § 103(a) as being unpatentable over either Hallenbeck (US Pat. No. 5,998,205) or Gregory (US 2003/0026789), taken with Fine (WO/98/13508), and further in view of McCormick I (US Patent NO. 5,666,178) or McCormick II (US Patent No. 5,801,029).

With regard to the Hallenbeck and Gregory patent and patent applications, respectively, Applicants refer the Examiner's attention to the statement made by Hallenbeck above. Clearly, this statement, coupled with the statement made by the Examiner, that neither

reference teach a tissue or cell specific promoter that is an E2F responsive promoter, supports the unobvious nature of Applicants' invention.

Regarding the Fine and McCormick I and II references, the reasons stated above explaining why they are not applicable references to support a 103 rejection, are equally relevant here.

Applicants believe that they have adequately and fully addressed all the Examiners rejections, and respectfully request that the Examiner expedite issuance of a letters patent. Should the Examiner believe otherwise, Applicants request the courtesy of an interview so that the inventors can personally state their case.

If the Examiner has any questions with regard to this amendment, the Examiner is encouraged to call the undersigned at: 510:262-8710.

Extension of Time Pursuant to 37 C.F.R. § 1.136(a)

A Petition for Three Month extension of time is being filed concurrently with this response. Applicant respectfully requests a 3 -month extension of time to file a Response to the Final Office Action mailed December 22, 2003. The extended period expires on June 22, 2004.

The Commissioner is authorized to charge any fees associated with this communication to Deposit Account No. 15-0615 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: June 22, 2004

By: Gregory Giotta
Gregory Giotta, Ph.D.
Reg. No. 32,028

ONYX Pharmaceuticals, Inc.
3031 Research Drive
Richmond, California 94806
Telephone (510) 262-8710
Facsimile (510) 222-9758